Overview and Role in Intramural Research Program Compliance with FDAAA

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DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

Agenda

- What is FDAAA
- Registering Protocols (What and How)
- Updating Protocol Information
- Submitting Results (What's Required)
  - Process for Submitting Results
- Complying with the Law (OPS/IRP)
  - Current
  - Future
- Overview of OPS

FDAAA, Public Law 110-85

- FDA Amendments Act, Enacted Sept 27, 2007
- Purpose: Increase transparency in both the conduct and reporting of clinical trials-“to provide more complete results information and to enhance patient access to and understanding of the results of clinical trials”
- Required Trial Registration of all Phase II-IV drug and device trials within 21 days of enrollment (Dec 2007)
  - NIH/IRP requires registration of ALL clinical research (some exceptions)

FDAAA, Public Law 110-85 (cont)

- Requires NIH to set up a basic results database of all Applicable Clinical Trials (ACTs) to include 2 tables

  1) Demographic and baseline characteristics sample (for each arm), including the number that dropped out, and the number excluded from analyses.

  2) Primary and secondary outcome measures for each arm, “including the results of scientifically appropriate tests for the statistical significance of such outcome measures.”
- Develop Adverse Events database
- Adds enforcement provision (stiff penalties)
- Expansion of results by Rulemaking (Sept 2010;NPRM) to consider:
  - Include unapproved drugs and devices
  - Include summary information without being ‘misleading’
  - Modification to the basic results information
  - Extend reporting to 18 months

Who is the Target Audience?

- PI and Clinical Research Team
- Medical Researchers in same field
- Medical Researchers in other fields
- Other Readers of the medical literature
- Science Writers
- Lay Public (readers of consumer health literature)

"to provide more complete results information and to enhance patient access to and understanding of the results of clinical trials"

Basic Requirements of FDAAA

1. Registration of Applicable Clinical Trials (ACTs) within 21 days of enrollment of the first participant.

2. Results reporting for ACT with an approved drug within 12 months of the primary completion date by the “responsible party”.

Definitions you should know:

- **ACT:** interventional studies, greater than a phase I study (includes approved drug, biologic, or device or an IND/IDE), and at least 1 site in the US, that were ongoing as of 12/26/07.

- **Primary Completion Date:** The date the final subject will be examined or an intervention received for the purposes of final collection of data for the primary outcome.

- **Responsible Party (RP):** Individual responsible for registration and results reporting.
  - IND/IDE holder
  - If no IND/IDE, the “initiator” of the trial
  - Sponsor or the PI, if designated by the Sponsor

More Definitions

- **Interventional:** Studies in human beings in which individuals are assigned by an investigator, based on a protocol to receive specific interventions. May/may not be random assignment.

- **Observational:** Studies in human beings in which biomedical and or health outcomes are assessed in pre-defined groups of individuals. Subjects in the study may receive diagnostic, therapeutic, or other interventions, but the investigator does not assign specific interventions to the subjects.

- **Clinical investigation:** When one or more subjects are prospectively assigned to specific *interventions* according to a protocol to evaluate the effects of the intervention on biomedical or health-related outcomes-ONLY interventional studies are clinical investigations

- **Not a clinical investigation**: When a drug is administered or provided to a patient as part of routine medical care, not assigned to interventions, and not under a study protocol, where the health care provider only observes and records the effects of the use of a marketed drug is not considered a 'clinical investigation' (Natural History)

Elaborated Definitions

Phase not equal to phase I:

- Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans as well *as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.*

- Bioequivalency, pharmacokinetics, pharmacodynamics, are considered phase I

- Phase I/II studies are not considered phase I and may be subject to results reporting.*

- *Except when study stops after phase I, and does not progress to phase II. Update phase information with OPS

What Gets Registered?

- Clinicaltrials.gov – all protocols with the exception of:
  - Interventional studies that are an ACT and the NIH is not the responsible party
  - Observational studies that received an exception from posting by NIH CC Director
  - Protocols posted by the coordinating site
- Search the Studies
  - Active studies at the NIHCC
  - Accrual status is recruiting or following participants

How are Protocols Registered

- OPS registers protocols on behalf of the IRP
- Information collected from:
  - Initial Protocol Application
  - Protocol
  - IRCT.gov email sent at time OPS completes the IR
    - Collects additional data elements required and not captured
- Nightly feed sent to clinicaltrials.gov

Protocols Posted by NIHCC

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
Advanced Search | Help | Studies by Topic | Glossary

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Search Results > Study Record Detail Text Size

Trial record **1 of 1** for: 06-c-0169
Previous Study | Return to List | Next Study

Natural Killer Cells Plus IL-2 Following Chemotherapy to Treat Advanced Melanoma or Kidney Cancer

This study has been completed.

Sponsor:
National Cancer Institute (NCI)

Information provided by:
National Institutes of Health Clinical Center (CC)

ClinicalTrials.gov Identifier:
NCT00328861

First received: May 20, 2006
Last updated: August 21, 2012
Last verified: August 2012
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

Background:

- Natural killer (NK) cells are large lymphocytes (a type of white blood cell) that are important in the immune response to cancer.

Updating Protocol Information

- Nightly feed from Protrak
  - Continuing review/Amendments
  - Request of research team
    - CC_Protocol_Services@cc.nih.gov

- If ownership of the protocol record has been transferred in the PRS, responsibility defaults to RP/designee

Basic Results Reporting

- Basic results reporting is required for all “approved” products (drugs, devices, biologics)
- “Approved” products are those which are approved by the FDA for at least one use, regardless of whether that use is studied in the trial
- A trial is not considered an ACT if there are no US sites and the product is not manufactured in the US. (International trials)

Basic Results Reporting: Entery of Results

Protocol Registration System (PRS)
Data arranged in Tabular format (Required by FDAAA)

- Logical table structure
- Modules for entering Results Data
- Measure Title/Description and Units of Measure consistent
- Complete scale information
  - Construct and domain
  - Best/worst values
  - “Units on a scale” if no other units
- Data ‘appear’ valid

Basic Results Reporting: What To Report

- Participants Flow
- Baseline Measurements
- Outcome Measurements
- Administrative Information
- Adverse Events

Posting Results on ClinicalTrials.gov

NLM Established the Format for Data Entry

Baseline Measures (Data Needed; tabular format)

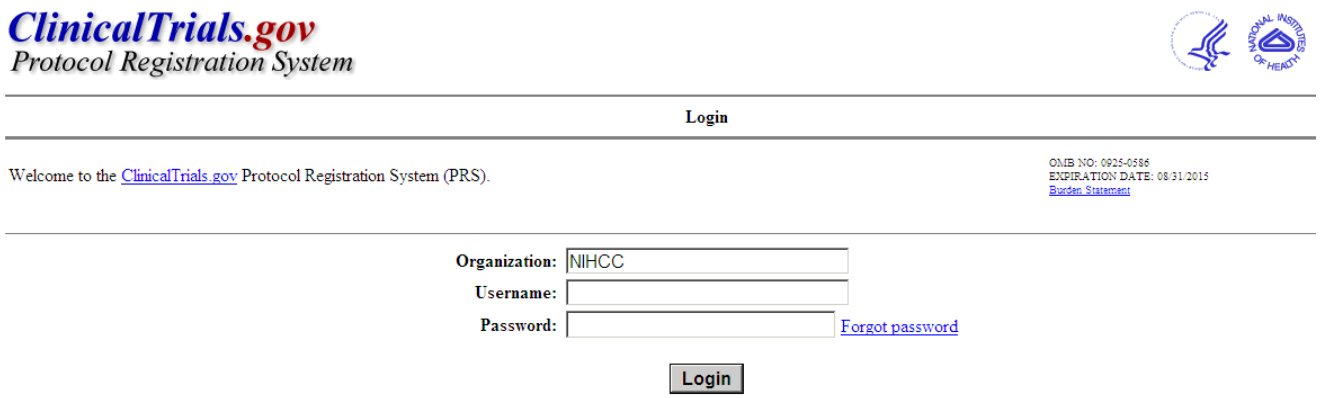
	Arm Title*	Arm Title*	Total
	Arm Description*	Arm Description*	
Overall Number of Baseline Participants*	# participants	# participants	*[calculated]*
Baseline Measure Title*			
Baseline Measure Description			
Units of Measure*			
Measure Type* (select one)			
Number			
Mean			
Median			
Least Squares Mean			
Geometric Mean			
Log Mean			
Measure of Dispersion* (select one)			
Not Applicable (when Measure Type = Number)	NA	NA	
Standard Deviation			
Interquartile Range (25th, 75th)			
Full Range (low value, high value)			

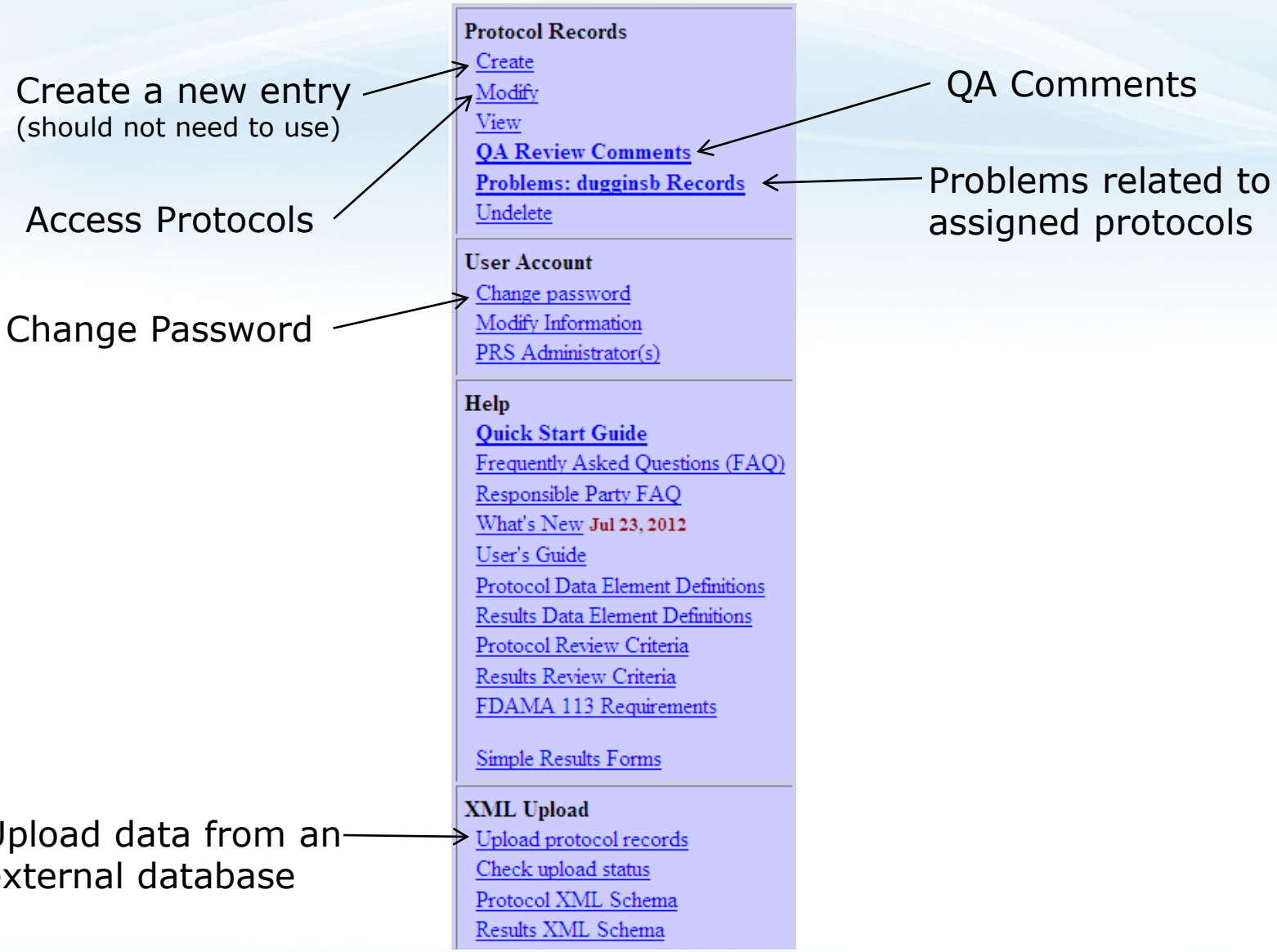
Reporting of Adverse Events

- Both serious and non serious AEs
- Both anticipated and unanticipated events
- Total number affected
  - By organ system
  - Type of approach to ascertain AE
- The current law sets a threshold of 5% for reporting non-serious AEs
- No guidelines for terminology

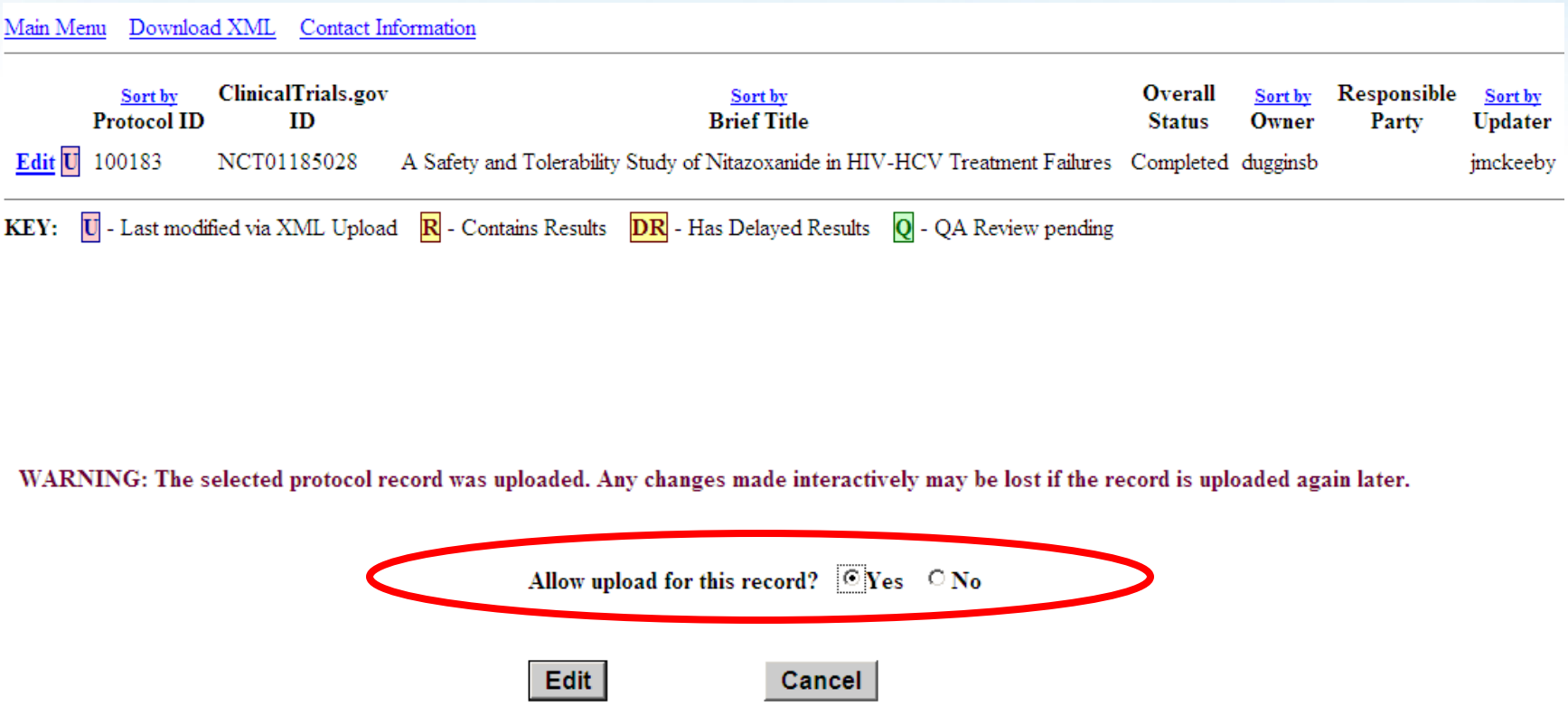
Submitting Results

- Time-frame: one-year from the primary completion date
  - Confirmation from the FDAAA IC Contact, RP, PI or designee
  - Update in Accrual Status to “Completed Study; Data Analyses”
- Transfer Ownership of Protocol Record
- Nightly updates to Clinicaltrials.gov cease at this time




Create a new entry
(should not need to use)
Access Protocols
Change Password
Upload data from an external database
QA Comments
Problems related to assigned protocols
Protocol Records
Create
Modify
View
QA Review Comments
Problems: dugginsb Records
Undelete
User Account
Change password
Modify Information
PRS Administrator(s)
Help
Quick Start Guide
Frequently Asked Questions (FAQ)
Responsible Party FAQ
What's New Jul 23, 2012
User's Guide
Protocol Data Element Definitions
Results Data Element Definitions
Protocol Review Criteria
Results Review Criteria
FDAMA 113 Requirements
Simple Results Forms
XML Upload
Upload protocol records
Check upload status
Protocol XML Schema
Results XML Schema

Getting Started



Change Record Status

Main Menu | Select | Preview | Spelling | Edit All | **Problems** | Copy | Download XML

Title: A Safety and Tolerability Study of Nitazoxanide in HIV-HCV Treatment Failure...

Optional Actions: Reset to Completed | Reset to In-Progress

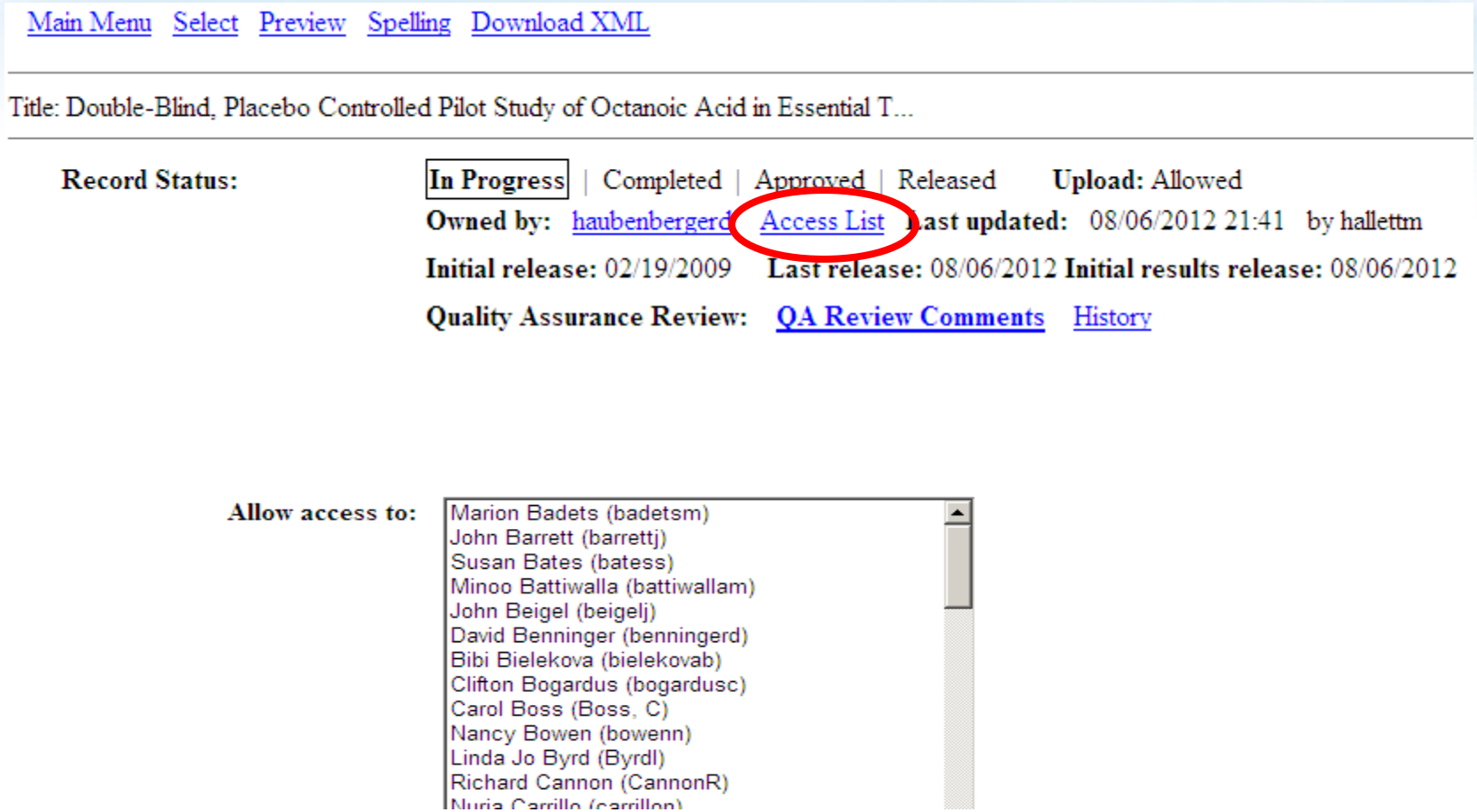
Record Status: In Progress | Completed | Approved | **Released** **Upload:** Allowed [Set...]

Owned by: Mitchellkjj Access List **Last updated:** 09/19/2012 04:17 by jmckeeby

Initial release: 08/18/2010 **Last release:** 09/19/2012 Download Receipt (PDF)

Quality Assurance Review: REVIEW COMPLETED

Access to Others



Warning, Alerts & Errors

Edit **Responsible Party:**

⚠ **WARNING: Responsible Party has not been entered.**

NOTE: Responsible Party was entered in the old format as Shyamasundaran Kottilil, M.D./National Institute of Allergy and Infectious Diseases

Review Board: Approval Status: Approved
Board Name:
Board Affiliation:
Phone: Email:

⚠ **ALERT: Approval Number: data not entered.**
⚠ **ALERT: Board Name: data not entered.**
⚠ **ALERT: Board Affiliation: data not entered.**
⚠ **ALERT: Neither Board Phone nor Email was entered.**

STOP **ERROR: An Outcome Measure Time Frame has not been entered.**
STOP **ERROR: The Number of Participants Analyzed has not been entered for an Outcome Measure group.**
STOP **ERROR: The Number of Participants Analyzed has not been entered for an Outcome Measure group.**
STOP **ERROR: A Measure Number of Central Tendency Value has not been entered.**
STOP **ERROR: A Measure Number of Central Tendency Value has not been entered.**

ERROR messages indicate serious problems that need to be addressed.

Approve Results

Main Menu | Select | Preview | Spelling | Edit All | **Problems** | Copy | Download XML

Title: A Safety and Tolerability Study of Nitazoxanide in HIV-HCV Treatment Failure...

Optional Actions: Reset to Completed | Reset to In-Progress

Record Status: In Progress | Completed | Approved | **Released** **Upload:** Allowed [Set...]

Owned by: Mitchellkjj Access List **Last updated:** 09/19/2012 04:17 by jmckeeby

Initial release: 08/18/2010 **Last release:** 09/19/2012 Download Receipt (PDF)

Quality Assurance Review: REVIEW COMPLETED

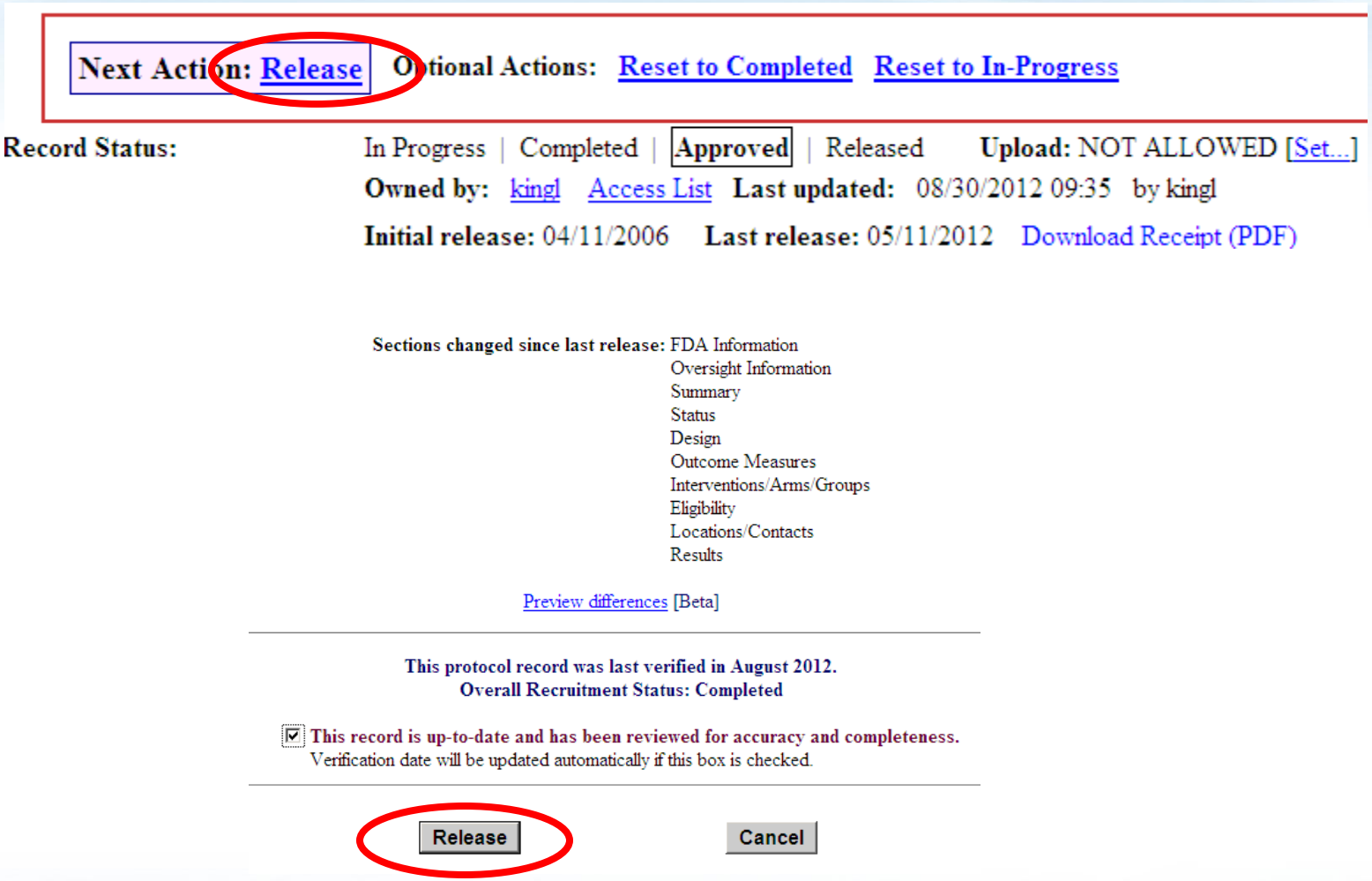
Next Action: Approve **Optional Actions:** Reset to In-Progress

Record Status: In Progress | **Completed** | Approved | Released **Upload:** NOT ALLOWED [Set...]

Owned by: kingl Access List **Last updated:** 08/30/2012 09:35 by kingl

Initial release: 04/11/2006 **Last release:** 05/11/2012 Download Receipt (PDF)

Release Results - Only when RP has been modified



Submission with Errors

Errors in protocol or results data. See messages below.
Additional information may be required per US Public Law 110-85. See WARNING messages below.

- ERROR: An Outcome Measure Time Frame has not been entered.
- ERROR: The Number of Participants Analyzed has not been entered for an Outcome Measure group.
- ERROR: The Number of Participants Analyzed has not been entered for an Outcome Measure group.
- ERROR: A Measure Number of Central Tendency Value has not been entered.
- ERROR: A Measure Number of Central Tendency Value has not been entered.

Questions related to submission of results: register@clinicaltrials.gov

Delayed Submission of Results

- Certification
  - Certify Initial Approval
  - Certify New Use
- Extensions

NLM QA Review of Results

- After all data have been entered, it undergoes QA review by NLM (<30 days)
  - Two reviewers
  - RP will receive QA email, with comments
  - May require modification or corrections
  - Data posted once ‘clean’

QA Review
Average times through **QA=2.6**

IRP Compliance - Current

- Penalties
  - Delinquent results subject to $10,000 fine – NIH protected by Tort Claims
  - “Public humiliation” - posting on web that study is Not Compliant with FDAAA Requirements
  - FDA auditing/contacting program official for results delinquent
  - While FDA is considering what penalties should be exacted, it is left to the discretion of the SD as to what actions should be taken for continuing non-compliance
- Bi-monthly compliance reports
  - IC representative and CD
  - IRP summary report to DDIR, DDICR, NIH CC Director, IRP Compliance Officer
- Overdue Results Summary sent bi-monthly to branch/lab chief, CD and Inst Rep

IRP Compliance - Future

- Notifications
  - Transfer ownership of record when Primary Outcome met
  - 30-60 days prior to results deadline
  - Date results due
  - ? Months after results are overdue

- Website for Intramural Compliance
  - Hints/tips to access and update protocol record in PRS
  - Algorithm for determining if a protocol is an ACT
  - Downloading data from BTRIS

So How Are We Doing?

	Registered ACT[1]	Number of ACTs Requiring Results[2]	"Primary Completion Date Met(<=09/24/12)" or date has past and not been updated	Registered ACTs that are within the one-year reporting time-frame	Registered ACTs that are Overdue for results reporting[3]	Submitted Results Records (undergoing Quality Review by NLM)	Results Posted[4]
NIH Intramural	429	419	198	37	43	33	85
			47%	19%	22%	17%	43%
July 2012	427	415	193	39	58	34	62
			47%	20%	30%	18%	32%

Role of IRP in Complying with FDAAA

- IRP Compliance Officer
  - reviews bi-monthly reports generated by OPS
  - Contacts investigators who exceed submission of results deadline by>1 yr with no attempt to enter data
- ACT Review Committee: reviews protocols where it is indeterminate if the study meets ACT criteria
- The consequences of continued non-compliance will be up to the discretion of the SD

Overview Of OPS

EXTRA CREDIT!

Intramural Research Program
Our Research Changes Lives

one program
many people
infinite possibilities

Overview of OPS

- Complete the processing of actions
  - 410 protocol actions on avg. per month
  - 500-600 consent on avg. per month
- Post consent documents to NIH Clinical Research Studies Active consent/Assent Documents website
  - Short-form consents - 33 different languages
- Maintain Intramural Research Protocol Repository- Protrak
  - Generate ad-hoc reports
  - Respond to Inquiries
  - Notify CC Departments Monthly of new/terminated protocols
  - Inactivate protocols that are overdue – data flows to CRIS and prevents new patient admissions

Overview of OPS

- Generate Protocol Accrual Reports
- Update protocol websites via feed to the CC Data Warehouse
  - Clinicaltrials.gov
  - NIH Clinical Research Studies
  - Protocol Query System
  - BTRIS
- Liaison for Clinicaltrials.gov
  - FDAAA - Monitor for Compliance
  - Register Protocols
  - Collect required information for registration in accordance with FDAAA and FDAMA
  - PRS database administrators for IRP

Overview of OPS

- Intramural Representative for Compliance with NIH Policy of the Inclusion of Women and Minorities in Research
  - Analyze policy implementation
  - Generate data annually reflecting participant accrual by Ethnicity-Race-Gender for Congressional reporting

Thank You
QUESTIONS?

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